548228

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
06/548,228	11/02/83	REDDY	

FISH & RICHARDSON
ONE FINANCIAL CENTER

EXAMINER	
ART UNIT	**PAPER NUMBER**
	16

DATE MAILED:

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on Oct. 14, 1986 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1, 3, 5, 7, 9-15, 17-31, 33-44 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1, 3, 34 and 35 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 5, 7, 9-15, 17-31, 33 and 37, 38 and 40-44 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.

8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).

10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.

12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an enabling disclosure. Applicants' declaration of November 11, 1985 has been considered; however it is unclear whether applicants have satisfied the requirements of MPEP 608.01(p) (C) in regard to permanence and availability to the public. In regard to permanence, a period of 30 years after the deposit, 5 years after the last request or the enforceable life of the patent, whichever is longer has been found to be adequate. The deposits should be available to the Commissioner during pendency and all restraints upon availability should be irrevocably removed upon issuance of a patent. Applicants should also indicate that they will replace the deposits should they mutate or become nonviable. Assurance of compliance may be in the form of an averment under oath or declaration.

Claims 5, 7, 9-15, 17-31, 33, 37, 38 and 40-44 are rejected under 35 U.S.C. 112, first paragraph, for the

reasons set forth in the above objection to the specification.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. 112, first paragraph, as the specification as originally filed, does not provide support for the invention as is now claimed.

It is unclear from reviewing the ATCC papers in support of the preliminary amendment of July 24, 1984, that the deposits CRL8400 and CRL8401 contain plasmids PRF 398 alpha t_{α} and pRF375 and pRF398 respectively. A clarification is requested.

Claims 28-30 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the above objection to the specification.

Claims 5, 7, 9-15, 17-21, 33 and 42-44 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited in accordance with the specification on pages 1-3 and 17-22. See MPEP 706.03(n) and 706.03(z).

Applicants have limited claims 5, 33 and 42-44 to host eucaryotic cells; however, eucaryotic cells include yeast cells as well as mammalian cells. Applicants have only shown mammalian cells as host for the vectors encoding the alpha and/or beta subunits of LH or hCG. It is maintained that applicants' specification does not support the breadth of the claims to encompass all eucaryotic cells. Additionally, the host appears to be important in the proper processing of the glycoprotein hormones and only references which use mammalian cells as hosts show proper assembly of complex proteins resulting in active biological proteins. Applicants' arguments are not persuasive.

Claims 5, 7, 10-15, 17, 19, 20 and 22-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 17 and 19 are indefinite in failing to provide proper antecedent basis for "the alpha and beta subunits" and "said heterodimeric hormone" in the claims from which these claims depend. Claim 20 is indefinite in failing to provide proper antecedent basis for "said first and said second vectors". Claims 17 and 19 are indefinite in depending from canceled claim 16. It is

requested that applicants be consistent and refer to the subunits as the alpha and beta subunits in all claims. Claims 5 and 7 are confusing in that claim 5 recites encoding one or both subunits and claim 7 recites encoding for the second subunit. It is unclear that when claim 5 encodes for one subunit that subunit is the first subunit. It could rather code for the second subunit than the limitation of claim 7 would result in a cell with two vectors both encoding the second subunit. Claim 22 is indefinite and confusing in the recitation of "the two different subunits..."

Claims 5, 7, 9-15, 17-31, 33, 37, 38 and 40-44 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 and 29-32 of copending application serial no. 811,959 which is a continuation of application Serial No. 548,211, now abandoned. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the applications claim cells containing expression vectors and vectors coding for heteropolymeric proteins and methods for producing heteropolymeric proteins.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following is a quotation of 35 U.S.C. 103 which

forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 5, 7, 9-13, 17, 18, 21-25, 33, 37, 38 and 40-44 are rejected under 35 U.S.C. 103 as being unpatentable over Fiddes et al (1981), Fiddes et al (1980) and Pierce et al in view of Moriarty et al and Rice et al. Rice et al teach a mouse lymphoid cell line which is transformed with a plasmid containing the gene for the kappa light chain. The mouse cell inherently produced a gamma 2b heavy chain and subsequently assembled these heavy and light chains into a complete immunoglobulin. The other references are applied as in the previous office actions. In the absence of unexpected results, it would be obvious to one skilled in the art to clone the alpha and/or beta subunits of the human glycoprotein

hormones, hCG and LH, as taught by the Fiddes et al references, to produce biologically active assembled glycoproteins as suggested by Pierce et al, in a eukaryotic host cell as taught by Rice et al and Moriarty et al under the control of the SV40 late promoter, as a mere matter of inserting known DNA sequences into vector which will replicate in a eukaryotic cell, specifically a monkey cell.

Applicants argue, utilizing the declaration of Pierce, dated September 24, 1986, that the Pierce et al reference in no way renders obvious that two subunits of a hormone could be synthesized and made to associate to form an active hormone in a cell which is not specialized to make the hormone. This argument is not found to be persuasive especially in light of the additional teachings of Moriarty et al, which on pages 2609 and 2610, teach that P2 of HBsAg is glycosylated in the monkey cell hosts and the HBsAg is excreted into culture medium as 22 - nm particles with the same physical properties, antigenic composition and constiuent polypeptides as those found in patient sera with type B hepatitis. Further this reference teaches that when HBsAg was cloned in E. coli, the antigen was not glycosylated, assembled into particles or excreted from the bacterial host. This reference concludes that animal

cell expression systems will be useful where "the final gene product is modified and assembled into a complex biological structure". Rice et al also support the fact that mammalian cells are capable of assembling complex proteins in cells which do not normally produce these proteins. Further, in Elder et al cited as of interest, (See pages 329 and 330) other proteins, such as human growth hormone and rat proinsulin, in addition to HBsAg, are found to be appropriately modified in mammalian cells which do not ordinarily synthesize these products.

The Pierce et al declaration discussed a Lustbader et al abstract where when the alpha subunit is produced in a recombinant cell in the absence of the beta subunit it is not capable of combining with the beta subunit. Applicants' claims encompass producing both subunits in one cell. Therefore, these arguments are not deemed to be persuasive.

Claims 14, 19, 26, 27 and 30 are rejected under 35 U.S.C. 103 as being unpatentable over Fiddes et al (1981), Fiddes et al (1980) and Pierce et al in view of Moriarty et al and Rice et al and further in view of Reddy et al and Hamer et al.

Reddy et al, Hamer et al and the other references are applied as in the previous office actions. It would be obvious to one skilled in the art to clone the alpha

and beta subunits of the human glycoprotein hormones, hCG and LH as taught by the Fiddes et al references, to produce biologically active assembled glycoproteins as suggested by Pierce et al in a eucaryotic host as taught by Moriarty et al and further it would be obvious to put the alpha and beta subunits under two different known promoters such as the SV40 early promoter as taught by Reddy et al and the mouse metallothionein prometer as taught by Hamer et al.

Claims 15, 20, 28, 29 and 31 are rejected under 35 U.S.C. 103 as being unpatentable over Fiddes et al (1981), Fiddles et al (1980) and Pierce et al in view of Moriarty et al and Rice et al and further in view of Reddy et al, Hamer et al and Sarver et al. Sarver et al and the other references are applied as in the previous office actions. It would be obvious to one skilled in the art to clone the alpha and beta subunits of the human glycoprotein hormones, hCG and LH as taught by the Fiddes et al references, to produce biologically active assembled glycoproteins as suggested by Pierce et al in a eucaryotic host as taught by Moriarty et al and further it would be obvious to put the alpha and beta subunits under different promoters, such as the SV40 early promoter as taught by Reddy et al and the mouse metallothionein promoter as taught by Hamer et al. It

would be further obvious to include the known transforming region of bovine papilloma virus as taught by Sarver et al into to a vector to clone the alpha and beta subunits of the glycoprotein hormones in mouse cells.

It is noted that a declaration by Nancy Hsiung, dated December 10, 1985 was submitted to prove that applicants made their invention prior to October, 1983, the date of publication of the Ochi et al reference. It does not appear from the record that the Ochi et al reference was applied in a rejection. It is noted that Ochi et al was discussed in the interview on October 18, 1985. The Hsiung declaration is considered to be defective in that only the inventor Hsiung signed the declaration and no reasons were given as to why the other inventors did not sign the declaration (See MPEP 715.04). Additionally the accompanying laboratory notebook does not provide that a dimeric hCG was produced rather the declaration indicates that "column B, 'CM alpha beta', was later shown to produce biologically active dimeric hCG."

Any inquiry concerning this communication should be directed to Jayme A. Huleatt at telephone number 703-557-1096.

Jayme A. Huleatt:dm

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January 18, 1987

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ART UNIT 127